AFCROs

LES ENTREPRISES DE LA RECHERCHE CLINIQUE

EARLY ACCESS PATHWAY IN FRANCE: ALL YOU WANT TO KNOW

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Different pathways are dedicated to innovative drugs in France.
One of them, the system of early access has been reformed in July 2021.

What is early access about?

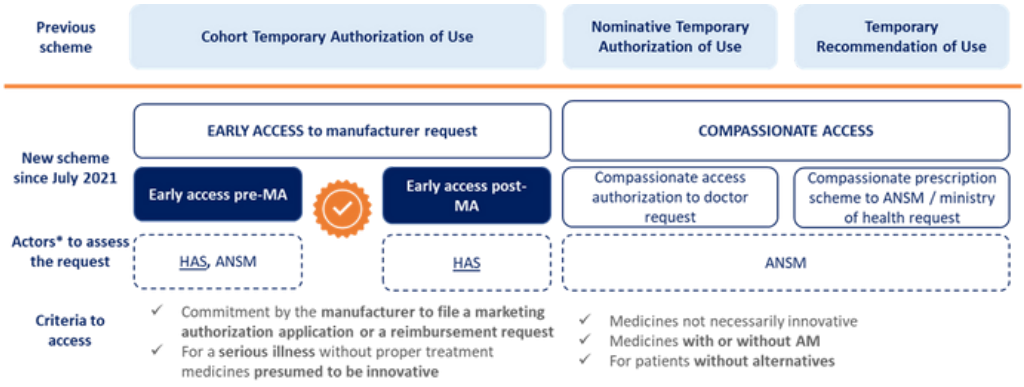
Early access authorization is enabling the early availability and reimbursement of a medicinal product indicated for a severe, rare or disabling disease, when specific conditions are met. This access scheme has been a possibility in France for a long time with the temporary authorization use (ATU) and has recently been revised as part of the reform of early access in 2021.

What is the reform about?

The goal of the reform was to:

- Simplify complex existing procedures and multiple stakeholders
- Speed up the time to access treatment for patients
- Secure the funding of theses access schemes for drug manufacturers, while securing financial sustainability of the health care system
- Enlarge real world data collection for innovation in considering them as mandatory as part of early access programs implementation

Synthesis of the main changes with the new reform on early access



*Underlined: new actor involved in the new scheme.
HAS : Haute Autorité de santé, ANSM : Agence Nationale de Sécurité du Médicament,
MA : Marketing Authorisation

When an early access can be asked within the market access strategy?

An early access can be asked for a drug **before the market authorization** (pre-MA) or **after the market authorization** (post-MA). The clinical development studies of the medicinal product in the indication considered for early access can therefore be at different stages of maturity: an early access can be asked as soon as preliminary clinical data reassure on efficacy potential of the drug while reassuring on the safety.

In which conditions an early access can be asked?

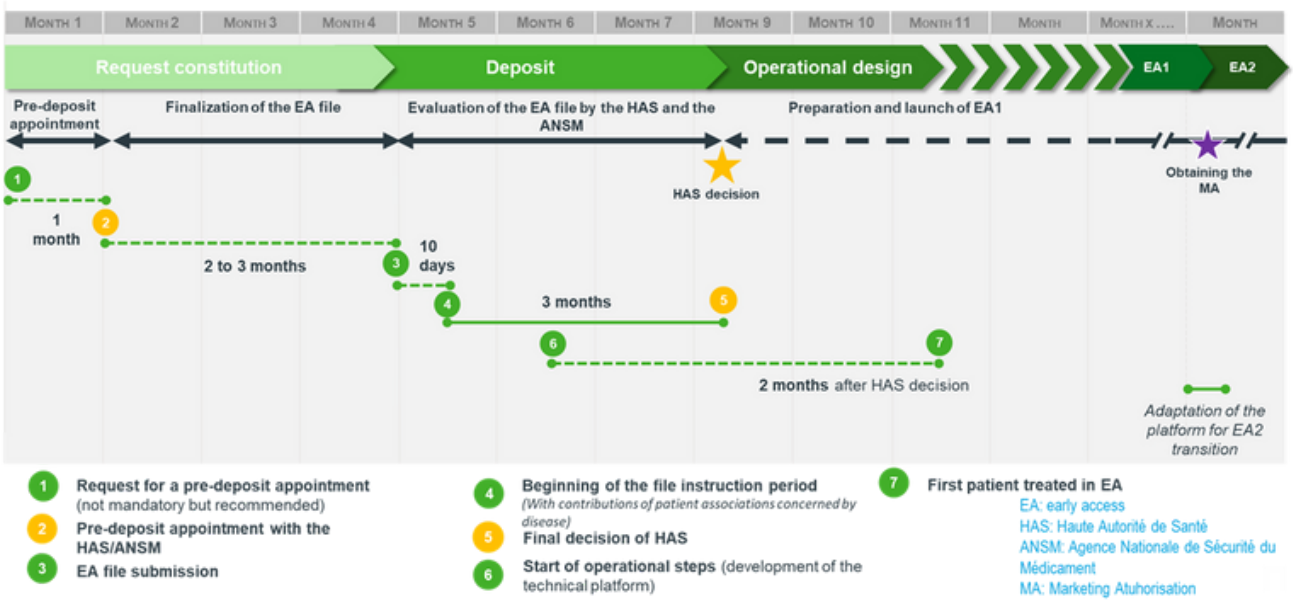
The new reform defines precisely **four eligibility criteria** to be filled to grant an early access. These criteria are evaluated by the HAS, with the approval of the ANSM confirming the strong presumption of efficacy and safety of the medicinal product in the case of a pre-MA early access.

Severe, rare or disabling disease	The severity of a disease or its disabling nature is assessed in view of the medical context based on: • The description of the symptoms and organ involvement • The mortality rate • The impact of the disease on patients' quality of life • The prevalence and incidence of the disease are used to support its rarity.
Presumed innovative nature	The presumption of innovation is assessed according to the development plan of the medicinal product and is compared to the existing relevant comparator(s), in relation to the resources available in the care strategy. The classification of presumed innovation does not influence the subsequent conclusions of the Transparency regarding the inclusion of the product candidate in the lists of products eligible for reimbursement.
Lack of appropriate treatment	In the early access processes, identifying the availability of right treatments for a certain disease in the market is essential. Indeed, when a new treatment already has alternatives on the market, the early access application can be/is denied. The lack of appropriate treatment ensures that no other relevant therapeutic option than the candidate is available for the patient in routine practice.
Impossibility to postpone treatment initiation	The assessment of the option to delay a treatment without involving a serious and immediate risk for the patient's health, is particularly based on whether an adequate treatment exists or not.

How does it work in practice?

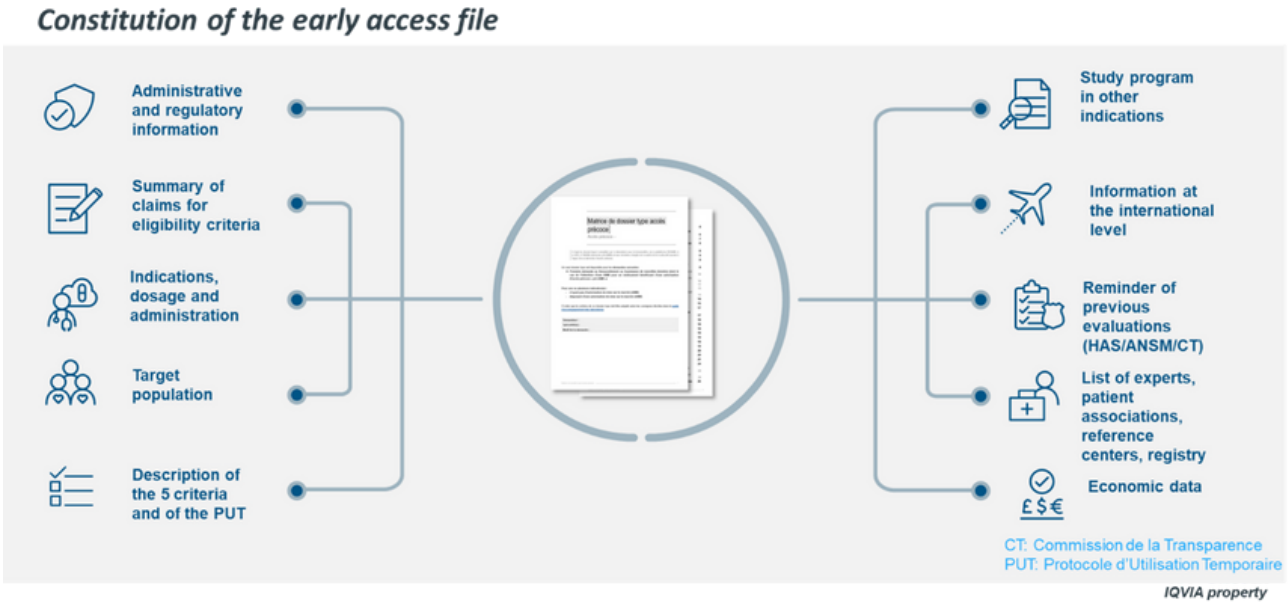
I**n practice**, timelines and deadlines are more predictable as they are framed in HAS doctrine and seem to be well respected (for more detailed information: https://www.afcros.com/publications/). To test the main objections and the probability of success, interactions with HAS and ANSM are possible for early-access pre-MA request and worth considering. After the complete application of the manufacturer, the HAS decision to grant or not an early access will be taken in a delay of a maximum of three months, excluding suspensions and extensions. Patients 'associations can contribute to the evaluation of the early access request by filling a questionnaire which will be taken into account by HAS. The authorization for early access is granted for maximum one year renewable.
The manufacturer must make the medicinal product available within a maximum period of two months following granting of the early access authorization.

Timelines for Early Access Implementation Process in France



What are the documents needed to develop the EA dossier to be submitted to the authorities?

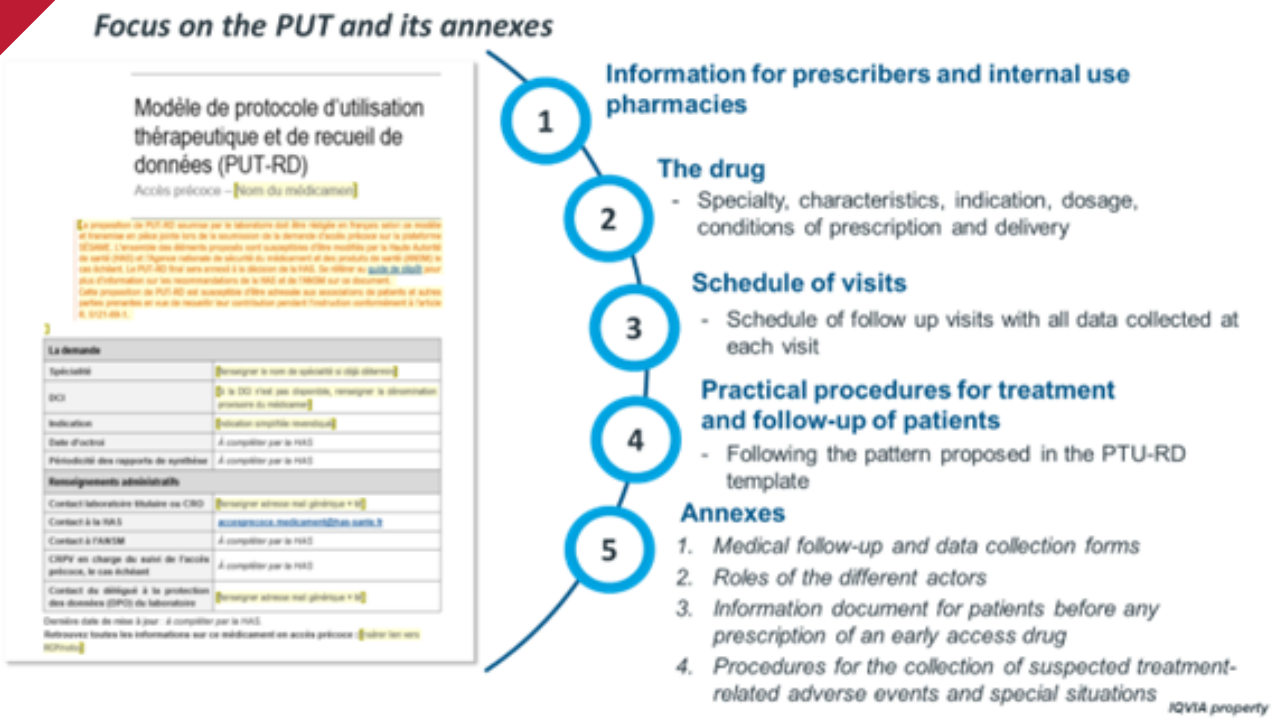
There is a template of dossier to be completed in French by the manufacturer for transmission, via the SESAME platform, to the HAS, to the ANSM (for pre-MA request) and to the ministers responsible for health and social security as a support of its request for early access. Of note new data may be submitted during instruction of the dossier, by the manufacturer or on the HAS/ANSM request.



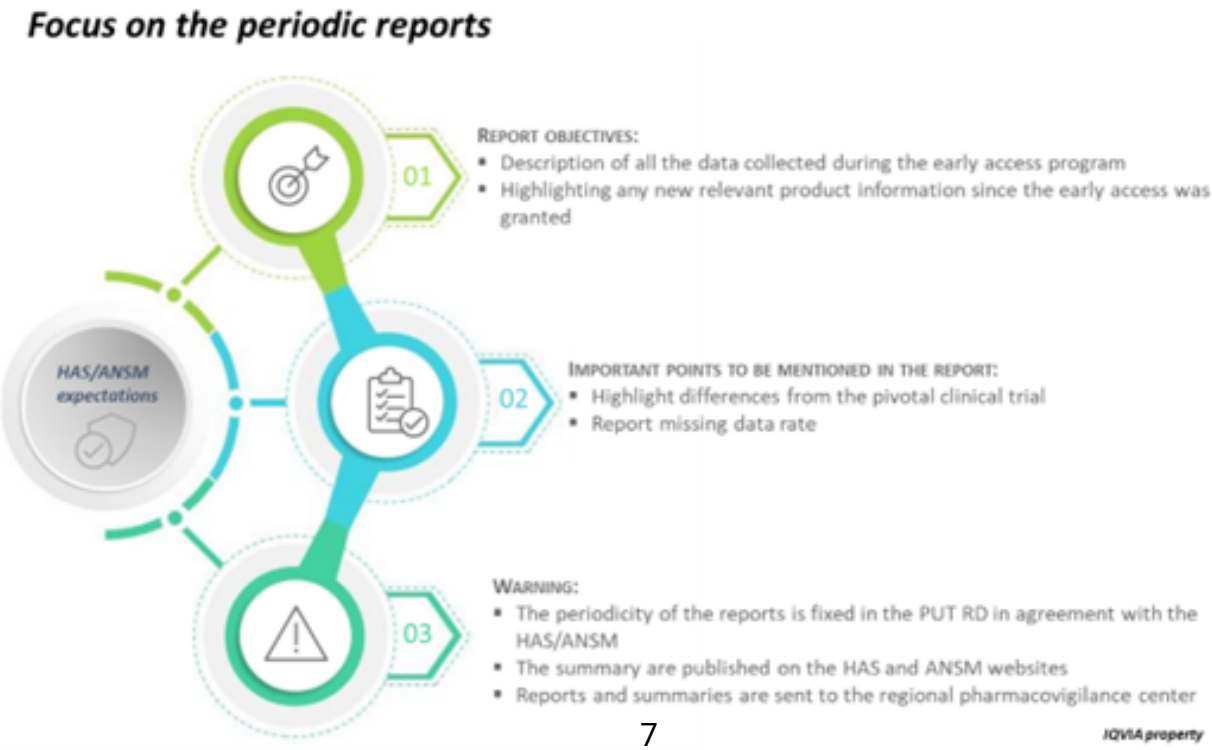
Early access authorization is subject to the manufacturer adherence to a **protocol for therapeutic use and data collection (PUT-RD)**, defined by HAS, in conjunction with ANSM where applicable, and annexed to the authorization decision.

This PUT-RD aims to organize monitoring of patients and to collect observational/real-life data in patients benefiting from a drug in early access authorization of a restricted number of variables regarding: patients characteristics, conditions of use, efficacy including quality of life (using a patient reported outcome measure) and safety.

If the early access authorization application for a medicinal product is made after the MA has been granted, the requirements in relation to data collection within the scope of the PUT-RD may be reduced where applicable.

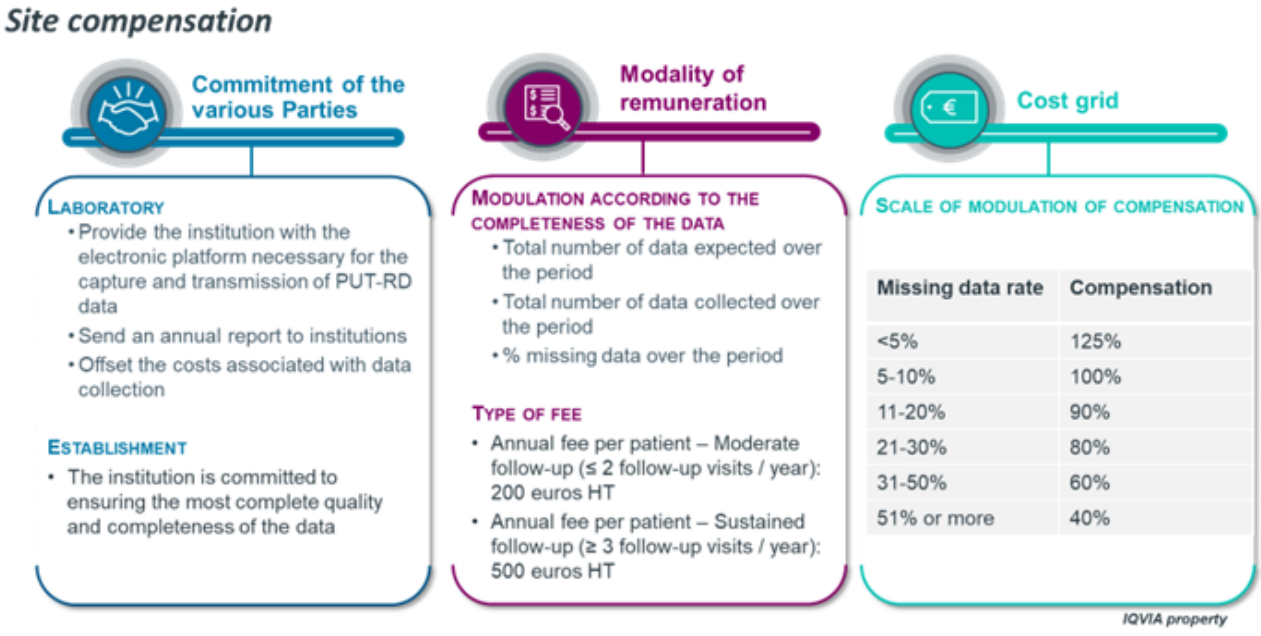


In addition to the PUT-RD, it is recommended that the manufacturer implement a **data management plan** as well as a **descriptive statistical analysis plan**. Both documents will be submitted to the authorities to complete the standard file.
The results of the data collection should be presented in a periodic report drafted by the manufacturer, according to a frequency defined by the HAS/ANSM and following the report template.



What are the additional requirements to collect data via the PUT-RD in France?

High quality data	Data collected through EAP should be exhaustive and accurate **with less than 10% of missing data**, it can support those clinical data HAS already has in order to be able to evaluate the drug
Site compensation	According to the HAS assessment doctrine, the manufacturer is expected to play an active role in data collection input and monitoring by providing the necessary resources to the medical teams concerned. The legislative and regulatory framework of EAP envisages the **setting up of a financial agreement between the manufacturer and site** that establishes the terms of compensation for the site. Indeed, a compensation modulation scale based on the completeness of the data entered will be applied. This step adds administrative complexity at site level.



Source data verification and on site monitoring not possible	Of note, early access programs are not considered as research studies and consequently are not covered by the French public health code. **In this context on site monitoring by external Clinical Research Assistant (CRA) is not possible** which makes the 10% missing data condition very challenging.
Favor the use of digital platforms via a single way of connection	With the same aim of improving data quality, HAS pushes toward the **use of digital platforms** with a strong multi-factor authentication to ensure traceability and decrease missing data for a simpler data collection. Since September 30th 2022, identification and authentication to all numeric tools dedicated to the products with early access authorization should be done via Pasrel/ Plage services implemented by ATIH.
Patient reported outcome	In addition, one of the new requirements in EAP is integration of the perspective of patients and users in the evaluation of health products because they have specific knowledge about their disease. Thus inclusion of a **PROM where patient feedback is essential**, particularly in incapacitating and severe diseases, is required notably for Pre MA early access programs. Patient questionnaire should fulfill the following conditions: validated French-language self-reported questionnaire, interpretable and specific to the investigated disease. Failing a validated specific self-reported questionnaire for the disease, a "Patient Global Impression Change" type question can be envisaged
Potential reuse of data for research purposes	HAS wishes to capitalize on pre-existing data and in particular those from the SNDS (National Health Data System). To this end, **it is recommended to design the data collection to facilitate linkage with data from the SNDS** upon request of the HAS. Database storage on the Health Data Hub is also encouraged
"Exploitant" status	Under the French legal framework, an operator who wants to market a medicinal product from and in France **should hold an Exploitant status** or partner with an Exploitant. The exploitant is accountable for: • distribution and marketing of the medicinal product onto the French market • medical information • pharmacovigilance

In addition, according to the CNIL referential applicable to the EAP, collected data should be stored on servers dedicated to store health data (HDS: hébergeur de données de santé).

What is the impact of an early access on the price of the product?

A pre-MA or post-MA early access authorization granted by the HAS means automatic funding by the national health insurance system. The price is freely fixed by the manufacturer with a complete coverage for hospitals. Some pay-back can occur after one year according to the observed turnover and pre-established scales. Finally, at the end of the price negotiations for a standard access to the product, pay-backs can be asked to the manufacturer according to the net price obtained or a reference price.

In conclusion

Early access program is an innovative process which allows large and fast access to medicine products under development. Nevertheless, setting up an early access implies numerous requirements and an important investment mainly from the manufacturer but also from the site where patients are treated. The time to market access and needed investment should be put in the balance.

In terms of investment, the strong requirement to collect data with high quality should be taken into account. It will be interesting to follow in the next years the use of these data in particular in the reevaluation of the drug concerned.